EXHIBIT 12

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
90/007,542	05/13/2005	6331415	10244P0010US	7585

7590 09/13/2005

EXAMINER	
ART UNIT	PAPER NUMBER

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DATE MAILED: 09/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Office Action in Ex Parte Reexamination	Control No. 90/007,542	Patent Under Reexamination 6331415	
	Examiner David J. Blanchard	Art Unit 1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

a☒ Responsive to the communication(s) filed on *13 May 2005*. b☐ This action is made FINAL.
c☒ A statement under 37 CFR 1.530 has not been received from the patent owner.

A shortened statutory period for response to this action is set to expire *2* month(s) from the mailing date of this letter. Failure to respond within the period for response will result in termination of the proceeding and issuance of an *ex parte* reexamination certificate in accordance with this action. 37 CFR 1.550(d). **EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c).** If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Information Disclosure Statement, PTO-1449.
3. ☐ Interview Summary, PTO-474.
4. ☐ _____.

Part II SUMMARY OF ACTION

1a. ☒ Claims *1-36* are subject to reexamination.
1b. ☐ Claims _____ are not subject to reexamination.
2. ☐ Claims _____ have been canceled in the present reexamination proceeding.
3. ☐ Claims _____ are patentable and/or confirmed.
4. ☒ Claims *1-36* are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ The drawings, filed on _____ are acceptable.
7. ☐ The proposed drawing correction, filed on _____ has been (7a)☐ approved (7b)☐ disapproved.
8. ☐ Acknowledgment is made of the priority claim under 35 U.S.C. § 119(a)-(d) or (f).
   a)☐ All b)☐ Some* c)☐ None of the certified copies have
   1☐ been received.
   2☐ not been received.
   3☐ been filed in Application No. _____.
   4☐ been filed in reexamination Control No. _____.
   5☐ been received by the International Bureau in PCT application No. _____.
   * See the attached detailed Office action for a list of the certified copies not received.
9. ☐ Since the proceeding appears to be in condition for issuance of an *ex parte* reexamination certificate except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte* Quayle, 1935 C.D. 11, 453 O.G. 213.
10. ☐ Other: _____

cc: Requester (if third party requester)

DETAILED ACTION

1. Claims 1-36 are pending and are considered in this re-examination.

2. The patent owner is reminded of the continuing responsibility under 37 CFR 1.565(a) to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving Patent No. 6,331,415 throughout the course of this reexamination proceeding. The third party requester is also reminded of the ability to similarly apprise the Office of any such activity or proceeding throughout the course of this reexamination proceeding. See MPEP §§ 2207, 2282 and 2286.

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1-36 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of US

Patent No. 4,816,567 in view of Axel et al (US Patent 4,399,216, issued 8/16/1983, Ids filed 5/13/05) and Rice et al (Proc. Natl. Acad. Sci. USA 79:7862-7865, December 1982, Ids filed 5/13/05) and Kaplan et al (EP 0 044 722, published 1/27/1982, Ids filed 5/13/05) and Accolla et al (Proc. Natl. Acad. Sci. USA 77(1):563-566, January 1980, Ids filed 5/13/05) and Builder et al (US Patent 4,511,502, issued 4/16/85).

The instant claims (US Patent 6,331,415 B1; the '415 patent) are drawn to recombinant processes, vectors and host cells for producing immunoglobulins comprising transforming a single host cell with a first DNA sequence encoding at least the variable domain of the immunoglobulin heavy chain and a second DNA sequence encoding at least a the variable domain of the immunoglobulin light chain and independently expressing said first and second DNA sequences so that immunoglobulin heavy and light chains are so produced as separate molecules in the transformed host cells wherein the DNA sequences can be present in different vectors or in a single vector that is the plasmid pBR322 and the host cell can be *E. coli* strain X1776 or S. *cerevisiae* and wherein the immunoglobulin heavy and light chains are expressed in the host cells and secreted therefrom as a functional immunoglobulin or is produced in insoluble form and subsequently solubilized and refolded in solution to form a functional immunoglobulin. Further, the claimed method for producing an immunoglobulin wherein the first and second DNA sequences further encode at least one constant domain derived form the same source or derived from a species or class different from that which the variable domains are derived and wherein the

variable domains are derived from one or more hybridomas. The claims are also drawn to vectors comprising said first and second DNA sequences encoding at least the heavy and light chain immunoglobulin variable domains and host cells, including mammalian host cells transformed with said first and second DNA sequences as well as insoluble particles of heavy and light chains or Fab region produced in *E.coli* or yeast cells (i.e., inclusion bodies). Additionally, the claims recite wherein the heavy and light chains are the heavy and light chains of an anti-CEA antibody and wherein the heavy chain is of the gamma family and the light chain is of the kappa family and wherein the method further comprises attaching the immunoglobulin to a label or drug.

Claims 1-7 of US Patent 4,816,567 (the '567 patent) are also drawn to recombinant processes, vectors and host cells for producing immunoglobulins, comprising preparing a DNA sequence encoding a chimeric immunoglobulin heavy or light chain having specificity for a particular known antigen wherein a constant region is homologous to the corresponding constant region of an antibody of a first mammalian species and a variable region is derived from a second different mammalian species, inserting the sequence into a replicable expression vector operably linked to a suitable promoter compatible with a host cell, transforming the host cell with said vector, culturing the host cell and recovering the chimeric heavy or light chain from the host cell culture, wherein the first mammalian species is human. Further, the claims are drawn to a composition comprising said chimeric immunoglobulin heavy or light chain having specificity for a particular known antigen as well as a replicable vector comprising

DNA encoding said chimeric immunoglobulin heavy or light chain operably linked to a promoter compatible with a suitable host cell and a recombinant host cell transformed with said vector. The claims in US Patent 4,816,567 do not specifically teach immunoglobulin expression on different vectors or on the same vector wherein the plasmid vector is pBR322 or obtaining the heavy and light chain immunoglobulin variable domains from at least one hybridoma or immunoglobulin expression in mammalian, bacterial (i.e., *E. coli* strain X1776) and yeast host cells or recovering the immunoglobulin produced in insoluble form (i.e., inclusion bodies) and subsequent solubilization and refolding in solution to form functional immunoglobulin molecules or an anti-CEA antibody or gamma heavy chains and kappa light chains or insoluble particles of heavy and light chains produced in *E.coli* or yeast or the attachment of a label or drug to the produced immunoglobulin. These deficiencies are made up for in the teachings of Axel et al and Rice et al and Kaplan et al and Accolla et al.

Axel et al teaches a process for inserting foreign DNA into eukaryotic cells by co-transforming the cells with this foreign DNA and an unlinked DNA that codes for a selectable phenotype not otherwise expressed by the cell (see column 3, lines 21-27). Axel describes the process as particularly suited for the transformation of DNA into eukaryotic cells for making immunoglobulins (see column 3, lines 31-36). Axel thus demonstrates the predictability of expression of multiple heterologous proteins in a single host cell. Axel also suggests the desirability of expressing immunoglobulins in mammalian host cells, and as intact (assembled) proteins.

Rice et al successfully introduced a recombinant rearranged murine kappa light chain gene construct into an Abelson murine leukemia virus (A-MuLV)-transformed lymphoid cell line, which is a cell line that already synthesized y2b heavy chain protein (see page 7862). Rice inserted the light chain gene into a plasmid, used this plasmid to transfect the cells, and then examined the polypeptides as well as the RNA produced by the cells (see pages 7863-7864, and Figures 2 and 3). Lastly, since the cells were producing both immunoglobulin chains, the cells were examined for the ability to assemble the chains into IgG molecules, leading to the observation that "[e]ssentially all of the κ chain produced in the K-2 cells appears to be assembled into IgG2b." (see page 7864). Thus, at the time of filing the application for the '576 and '415 patent it was known in the art that host cells could express "heavy or light chains," and that expression of both chains was routine, resulting in assembly into immunoglobulins.

Kaplan teaches that human hybridomas can serve as a useful source of mRNA encoding the antibody heavy and light chains to specific antigens. By using known molecular biology techniques, the mRNAs can be used for the generation of genes which, when inserted into the appropriate vector, can serve as a coding source for the production of proteins (see page 3, lines 4-9). In addition, Kaplan teaches that a variety of host cells, such as bacteria and yeast, may be used to express such recombinant immunoglobulin heavy and light chains (see page 10, lines 1-33).

Accolla et al teach CEA as an important tumor marker of human carcinomas and methods of making anti-CEA antibodies and anti-CEA antibodies as a standard reagent for CEA detection in human tissues and body fluids (see entire document, particularly the abstract).

Builder et al teach that the expression of exogenous or foreign proteins in bacteria or other host cells are frequently expressed as clumps of insoluble protein (i.e., refractile bodies) and Builder teaches a procedure for recovering, solubilizing and refolding such insoluble proteins (see entire document, particularly col. 2-6 and schemes 1 and 2).

a. The '567 patent claims a species of the genus claimed in the later '415 patent, causing obviousness-type double patenting.

Instant claims 1, 21 and 33 ('415 patent) are drawn methods for producing a genus of immunoglobulins and claim 1 of the '567 is directed to methods for producing "chimeric" immunoglobulin chains, which is a species of the immunoglobulin genus claimed in the later '415 patent. A second application containing a broader claim, more generic in character that the specific claim in the prior patent, typically cannot support a valid, independent patent. (i.e., species anticipates the genus). The same applies for the vector (claim 5) and host cell (claim 7) claims of the '567 patent and the corresponding claims 15-16 (vector) and 17-18 (host cell) of the '415 patent. Further, claim 1 of the '567 patent recites a chimeric immunoglobulin species of the sub-genus defined by claim 13 of the '415 patent and claims 2 and 6 of the '567 patent are directed to a

human constant region of the chimeric immunoglobulin, which is another example of a species within the genus claimed in the '415 patent. Applicant is reminded that the term "comprising" recited in claim 1 of the earlier '567 patent is inclusive or open-ended and does not exclude additional, unrecited elements or method steps (MPEP 2111.03). Thus, while the claims of the '567 patent embrace embodiments in which separate host cell cultures express either a chimeric heavy or a chimeric light immunoglobulin chain, the claims also read on embodiments in which one host cell culture expresses both the heavy and light chains, at least one of which is chimeric. Thus, claims 1-2 and 5-7 of the '567 patent read upon claims 1, 13, 15-18, 21 and 33 in the later '415 patent.

b. The '567 claims, alone or together with the prior art references, render the '415 claims obvious.

Claim 2 of the '415 patent recites that the heavy and light chain DNA sequences, including sequences encoding chimeric heavy or light chains, are on different vectors. Claims 3 and 25 of the '415 patent, which depend from claims 1 and 21, respectively, recite that the DNA sequences are present in a single vector. Claim 1 of the '567 patent reads on the process involving each of different vectors, or both DNAs on the same vector, since the process includes preparing each DNA sequence and inserting it in an expression vector for expression of each of the heavy and light chains before they are assembled into an immunoglobulin. Axel teaches transformed mammalian cells that produce multiple heterologous proteins on different vectors or on the same vector. Axel,

col. 6, lines 44-66 and col. 7, lines 3-9. Thus, '415 claims 2, 3, and 25 are obvious variants of '567 claim 1 in view of Axel.

Claim 4 of the '415 patent recites that the vector is a plasmid, and claim 5 recites that the plasmid is pBR322. A plasmid, particularly pBR322, is a type of vector within the scope of claim 1 of the 1567 patent. Axel and Kaplan both teach the use of plasmids, particularly pBR322, for expressing heterologous proteins. Axel, col. 8, lines 7-35; Kaplan, p. 10. Thus, '415 claims 4 and 5 are obvious variants of '567 claim 1 in view of Axel or Kaplan.

Claim 6 of the '415 patent recites that the host cell is a bacterium or yeast. Claim 7 recites that the host cell is *E. coli* (a bacterium) or S. cerevisiae (a yeast), and claim 8 recites that the bacterial host cell is *E. coli* strain X1776. Claim 19 recites that the host cell of claim 1 is a mammalian host cell. Claim 26 recites that the host cell is *E. coli* or yeast. Each of these host cells is a host cell within the scope of claim 1 of the '567 patent. Axel teaches mammalian host cells for expressing proteins, expressly including antibodies. Axel, col. 5, lines 3-7 and 24-28. Rice demonstrates expression of a recombinant immunoglobulin light chain in a mammalian host cell. Rice, p. 7863. Kaplan teaches bacterial and yeast host cells for expressing recombinant immunoglobulin chains. Kaplan, p. 10, lines 1-33. Thus, '415 claims 6-8, 19, and 26 are obvious variants of '567 claim 1 in view of Axel, Rice, and/or Kaplan.

Claims 9 and 29 of the '415 patent read on expression and secretion of an immunologically functional immunoglobulin. Axel teaches mammalian host cells for expressing proteins, expressly including antibodies. Axel, col. 5, lines 3-7 and

24-28. Rice demonstrates expression of a recombinant immunoglobulin light chain in a mammalian host cell. Rice, p. 7863. Thus, '415 claims 9 and 29 are obvious variants of '567 claim 1 in view of Axel and/or Rice.

Claim 10 of the '415 patent reads on solubilization of the insoluble heavy and light chains, followed by refolding, to form an immunologically functional immunoglobulin or fragment. '415 claims 27 and 28 read on deposition of insoluble heavy and light chain proteins and recovery of the insoluble proteins followed by solubilization in denaturant, respectively. '415 claim 31 recites recovering both the heavy and light chain and reconstituting the two chains to form an immunoglobulin. In each case, prior to formation of the immunoglobulin, one produces each of the heavy and light chains as separate molecules. Kaplan teaches bacterial and yeast host cells for expressing recombinant immunoglobulin chains (p. 10, lines 1-27) and Kaplan also describes rupturing the host cells, e.g., bacteria and yeast, isolating the heavy and light chains, and combining them under mildly oxidative conditions to promote refolding and disulfide bond formation (p. 10, lines 27-33). Builder et al teach that the expression of exogenous or foreign proteins in bacteria or other host cells are frequently expressed as clumps of insoluble protein (i.e., refractile bodies) and Builder teaches a procedure for recovering, solubilizing and refolding such insoluble proteins (see entire document, particularly col. 2-6 and schemes 1 and 2) and the '415 patentee also admits that reconstitution of immunoglobulins by refolding was known in the art (col. 13, lines 1-52). The separate chains are recovered separately for subsequent assembly. Thus, '415 claims 10, 27, 28,

and 31 are obvious variants of '567 claim 1 in view of Kaplan, Builder and the admitted prior art.

Claim 15 of the '415 patent recites that the vector comprises DNA sequences encoding at least the variable region of both the heavy and the light chain. Claim 16 specifies that the vector of claim 15 is a plasmid. Claim 5 of the '567 patent is directed to a vector, such as a plasmid vector, which encodes a chimeric immunoglobulin heavy or light chain. As discussed above, it includes a vector that includes DNA encoding both a heavy chain and a light chain. Axel and Kaplan teach the use of plasmids, particularly pBR322, for expressing heterologous proteins (Axel, col. 8, lines 7-35); (Kaplan, p. 10). Thus, '415 claims 15 and 16 are obvious variants of '567 claim 5 in view of Axel or Kaplan.

Claim 18 of the '415 patent is directed to host cells transformed with two vectors, one for the heavy chain and one for the light chain. Claim 20 specifies that the host cell of claim 18 is a mammalian host cell. Claim 7 of the 1567 patent is directed to host cells transformed with a vector encoding a chimeric heavy or light chain. A host cell of the '567 patent can be a mammalian host cell. As discussed above, the claim embraces host cells with two vectors, one for each chain, or one vector separately encoding both the heavy and light chains, so long as one or both are chimeric. Axel teaches mammalian host cells for expressing proteins, expressly including antibodies (col. 5, lines 3-7 and 24-28). Rice demonstrates expression of a recombinant immunoglobulin light chain in a mammalian host cell (pp. 7863). Kaplan teaches bacterial and yeast host cells for expressing recombinant immunoglobulin chains (p. 10, lines 1-33). Thus,

'415 claims 18 and 20 are obvious variants of '567 claim 7 in view of Axel and Rice, and claim 18 is further an obvious variant of '567 claim 7 in view of Kaplan.

Claim 22 of the '415 patent limits the method of claim 21 to making an anti-CEA antibody. CEA is a specific antigen within the general scope of a "particular known antigen" of claim 1 of the '567 patent. Accolla et al (Proc. Natl. Acad. Sci. USA, 77(1):563-566, January 1980) describes making anti-CEA monoclonal antibodies. The '415 patentee admits that anti-CEA antibodies are useful for the detection and potentially for use in treatment of tumors that have CEA at their surface. '415 patent, col. 16, lines 31-38, citing Gold et al, Journal of Experimental Medicine, 122:467, 1965 and van Nagell et al, Cancer Research, 40:502-506, March 1980. Thus, '415 claim 22 is an obvious variant of '567 claim 1 in view of Accolla or the admitted prior art.

Claim 23 of the '415 patent limits the method of claim 21 to that in which the heavy chain is of the gamma family, and claim 24 limits the method of claim 21 to that in which the light chain is of the kappa family. The terms "heavy chain" and "light chain" of claim 1 of the '567 patent read on gamma heavy chain and kappa light chain, respectively. Rice teaches expressing a recombinant kappa chain with an endogenous gamma chain in a host cell to produce an immunoglobulin molecule. Rice, pp. 7862 and 7864. Thus, '415 claims 23 and 24 are obvious variants of '567 claim 1 taken with Rice.

Claim 30 of the '415 patent recites that (1) the host cell is a gram negative bacterium and (2) the heavy and light chains are secreted into the periplasmic space of the host cell. A gram negative bacterium, such as *E. coli*, is a host cell

within the scope of claim 1 of the '567 patent. As pointed out above, claim 1 of the '567 patent also reads on secretion of the heavy or light chain, or both, including into the periplasmic space of a bacterium. Kaplan teaches bacterial and yeast host cells for expressing recombinant immunoglobulin chains (p. 10, lines 1-33). Thus, '415 claim 30 is an obvious variant of '567 claim 1 in view of Kaplan.

Claim 32 of the '415 patent is directed to an insoluble particle of heavy and light chains produced by the method of claim 27. Thus, claim 32 is directed to a composition of matter comprising immunoglobulin proteins. Claim 3 of the '567 patent is directed to a composition comprising a chimeric immunoglobulin heavy or light chain, whether it is soluble or insoluble. Kaplan teaches bacterial and yeast host cells for expressing recombinant immunoglobulin chains (p. 10, lines 1-33).) and Builder et al demonstrate that expression of exogenous or foreign proteins in bacteria or other host cells are frequently expressed as clumps of insoluble protein (i.e., refractile bodies) (see entire document). '415 patent, col. 12, lines 39-41. Thus, '415 claim 32 is an obvious variant of '567 claim 3 for insoluble chimeric heavy and/or light chain compositions in view of Kaplan and Builder.

Claims 34, 35, and 36 of the '415 patent recite that the processes of claims 9, 10, and 33 further include attaching the immunoglobulin to a label or drug. For the reasons provided above, claims 9, 10, and 33 are obvious variants of the '567 claims. Kaplan teaches the use of antibodies for site directed therapy wherein the antibody is attached to a drug or other therapeutic means as well as

the attachment of a radiolabel for localization (see page 8, lines 7-21). Thus, '415 claims 34, 35, and 36 are obvious variants of '567 claim 1, if necessary in view of Axel, Rice, Kaplan and Builder.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Consequently, the '415 patent claims are obvious variants of the '567 claims. They could have been (and had been) examined together and could have issued in the same patent. The delay in issuing the '415 claims significantly and inappropriately extends, by more than twelve years, the right to exclude others from practicing technology for recombinant expression of chimeric immunoglobulins. Filing a terminal disclaimer for the '415 patent so that it would expire at the same time as the first '567 patent would prevent the timewise extension of the patent right and, hence, cure the obviousness type-double patenting. *In re Vogel*, 422 F.2d 438, 164 U.S.P.Q. 619 (CCPA 1970); see MPEP 804.02.

This rejection of claims 1-36 was proposed by the third party requestor in the request for reexamination, and is being adopted essentially as proposed in the request in addition to the prior art of Builder et al.

5. Then third part request also proposes *Schneller*-type double patenting, however, this is not being adopted because *Schneller*, 397 F.2d 350, 158

U.S.P.Q. 210 is limited to a specific fact pattern that does not match the situation in the current reexam (MPEP 804).

Conclusion

6. No claim is allowed.

All correspondence relating to this *Ex parte* reexamination proceeding should be directed:

By Mail to: Mail Stop *Ex Parte* Reexam
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Any inquiry concerning this communication or earlier communications from the examiner, or as to the to the status of this proceeding, should be directed to the Central Reexamination Unit at telephone number (703) 308-9692.

David Blanchard
Art Unit 1643

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER